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(54) Title: PYROPHOSPHATE DIESTERS FOR TARTAR CONTROL

(57) Abstract

A tartar control oral composition containing carrier material and certain 1,2-substituted dihydrogen pyrophosphate compounds with flavorant, coolant, sweetener and/or antimicrobial components is described.

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PYROPHOSPHATE DIESTERS FOR TARTAR CONTROL

BACKGROUND OF THE INVENTION

The present invention relates to compositions comprising one or more phosphate derivatives, and carrier materials wherein the compositions are in a form suitable for oral or topical administration. These compositions preferably contain a safe and effective amount of one or more active materials such as those which provide nutritional, therapeutic, antimicrobial, pharmaceutical medicinal, and/or aesthetic benefit, and those commonly used in health care products.

A wide variety of flavor, coolant and sweetener agents are used in consumer and health care products today. Aesthetic qualities of these compositions such as taste, smell, mouthfeel, and after-taste are important concerns for consumer acceptability. Products with poor flavor, a bad after-taste or other negative aesthetics may limit consumer acceptability initially or over an extended period of time, thereby limiting consumer usage and compliance with treatment regimens.

An additional aspect of consumer acceptability and compliance is the consumer's perception of efficacy. Consumer satisfaction with a product is likely to be increased if some type of sensory signal exists to remind the consumer that the product is working after ingestion, administration or expectoration.

It has been discovered that phosphate derivatives comprising flavor, coolant, and/or sweetener components may be incorporated into oral or topical compositions to deliver pleasing aesthetics and high consumer acceptability. It has also been discovered that these compositions for oral or topical administration may be formulated to include a safe and effective amount of one or more actives. These compositions may provide sustained coolant, flavor and/or sweetener activity, depending on the particular derivative being used. These phosphate derivatives may also serve to improve the aesthetics of the compositions and provide a sensory signal to the user.

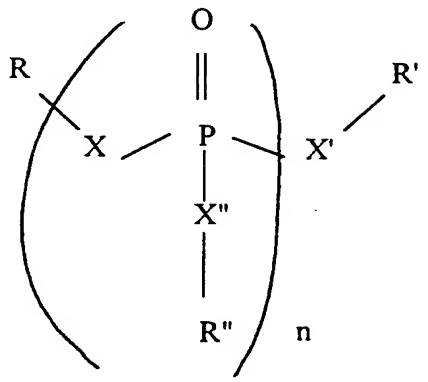
It has also been discovered that a specific type of phosphate derivative, 1,2-disubstituted-dihydrogen pyrophosphate and salts thereof, can be used in oral compositions to achieve several possible benefits: tartar control, improved taste (cooling and/or flavoring) and/or an antimicrobial effect (see section herein entitled "Pyrophosphate Diesters in Oral Compositions" and Example V on).

All percentages and ratios used herein are by weight, and all measurements are made at 25°C, unless otherwise specified.

SUMMARY OF THE INVENTION

The present invention relates to a tartar control oral composition, comprising, by weight of the composition:

(a) from about 0.001% to about 20% of one or more compounds of the formula;



where R and R' are independently selected from the group consisting of a coolant component, a sweetener component, an antimicrobial agent and a flavorant component; and where R or R' is hydrogen,

each R" is independently selected from the group consisting of R and R", an adherent group, M+, M++, C+, and hydrogen;

X, X', and X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

n is an integer greater than or equal to 1;

M+ and M++ are physiologically relevant metal cations; and

C+ is an organic cation; and

(b) from about 80% to about 99.999% of a carrier material;

and wherein further the composition is in a form suitable for oral administration.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention relates to a composition comprising one or more phosphate derivatives, and carrier materials wherein the compositions are in a form

suitable for oral or topical administration. These compositions also preferably contain a safe and effective amount of one or more actives.

The term "active" as used herein means an agent which provides an effect greater than an excipient such as agents providing nutritional, therapeutic, medicinal, antimicrobial, and/or aesthetic benefit, and those commonly used in health care products.

The phrase "suitable for oral or topical administration" as used herein means any formulation that is suitable for the convenient administration of the composition whereby the composition is intentionally swallowed, chewed, ingested, retained in the oral cavity for any period of time, placed in contact with internal mucous membranes of the body, such as those of the nose, mouth, or throat whether by direct or indirect application or inhalation to the nasal passages, or applied to the surfaces of the skin for therapeutic reasons or reasons other than for cosmetic benefit.

The phrase "a safe and effective amount", as used herein, means a sufficient amount of material to provide the desired benefit without undue adverse side effects (such as toxicity, irritation or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific safe and effective amount will vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), and the specific formulation and optional components employed.

The components for use in the present compositions and the preferred amounts to be utilized are described in detail hereinafter.

Phosphate Derivatives:

The present invention compositions contain one or more phosphate derivatives. These compounds may be formulated by phosphorylating a least one coolant, sweetener or flavorant component. These compounds also include linking at least one coolant, sweetener or flavorant component to an adherent component via a phosphate bridge. In addition, pyrophosphate and triphosphate groupings may be substituted for the phosphate group. Coolant, flavorant, or adherent components may also be linked to phosphorous via two functional groups or attachment sites. Furthermore, the phosphate derivatives described above may be bound via coulombic interaction with charged compounds or materials, including polymers.

The present compositions may deliver the desired coolant, flavorant and/or sweetener qualities through the action of the phosphate derivative itself. The compositions potentially provide a sustained effect through the release of the coolant,

flavorant and/or sweetener component from the molecule after cleavage by phosphatase enzymes.

The term "coolant component" as used herein refers to coolant compounds having a hydroxy, amino, or thiol functionality which is capable of forming an ester, amido, or thioester linkage with a phosphorus(V) atom. Preferred coolant components are selected from the group consisting of l-menthol, d-menthol, 3-l-menthoxypropane-1,2-diol ("TK-10"), menthone glycerol acetal ("MGA"), and l-menthyl lactate.

The term "flavorant component" as used herein refers to flavorant compounds having a hydroxy, amino, or thiol functionality which is capable of forming either an ester, amido, or thioester linkage with a phosphorus(V) atom. Preferred flavorant compounds are selected from the group consisting of methyl salicylate, eugenol, vanillin, thymol, cinnamaldehyde glycerol acetal ("CGA"), and linalool.

The term "sweetener component" as used herein refers to sweetener compounds having a hydroxy, amino, or thiol functionality which is capable of forming either an ester, amido, or thioester linkage with a phosphorus(V) atom. Preferred sweetener components are saccharin, mannitol, sorbitol, glucose, sucrose, fructose, and neohesperidin dihydrochalcone.

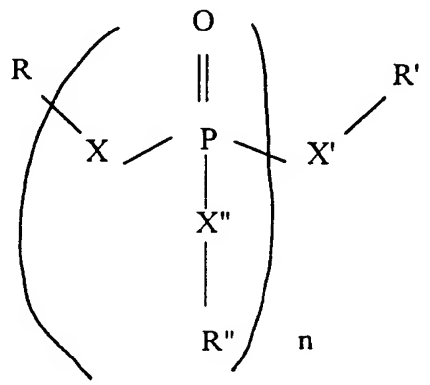
The term "adherent component" as used herein refers to either monomers, oligomers, or polymers having hydroxy, amino, or thiol functionalities which are capable of forming either ester amido, or thioester linkages with phosphorus(V) atoms. The monomers, oligomers, or polymers may also possess additional hydroxy, amino, or thiol groups which may either remain unsubstituted or be linked via ester amido, or thioester linkages to a phosphorus(V) atom which is also attached to a coolant, flavor, or active portion. Preferred compounds are selected from the group consisting of C12-C18 diacyl glycerol, partially hydrolyzed vinyl acetate/ethylene copolymer, cellulose, chitin, glucose, glucosamine, silica gel, glycerol, and methyl vinyl ether-maleic acid.

The terms "M+" and "M++" as used herein refer to physiologically relevant metal cations. The phrase "physiologically relevant metal cations" as used herein refers to metal cations that are significant to the organic or bodily processes of a human or lower animal. Preferred "M+" cations are sodium and potassium. Preferred "M++" cations are calcium, zinc, and magnesium.

The term "C+" as used herein refers to an "organic" cation. An "organic" cation as used herein refers to cations that contain positively charged nitrogen, phosphorous, oxygen, or sulfur atoms. Such cations may contain more than one positively-charged site and in the case of oligomers or polymers containing nitrogen,

phosphorous, oxygen, or sulfur atoms, many positively-charged centers may exit. Preferred "organic" cations include ammonium, protonated amines such as protonated glucosamine, and partially or fully protonated amine-containing polymers such as protonated chitosan.

The phosphate derivatives of this invention are represented by the following formula:



In the above formula,

R is selected from the group consisting of a coolant component, a sweetener component, and a flavorant component;

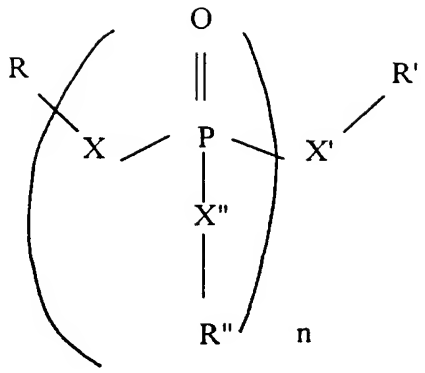
R' and R" are independently selected from the group consisting of R, an adherent component, M+, M++, C+, and hydrogen;

X, X', and X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur; and

n is an integer from 1 to 3.

In addition, R' may equal R", preferably wherein R' and R" are selected from the group consisting of calcium, zinc, manganese, and magnesium.

Preferred phosphate derivatives have the formula:



In the above formula:

R is selected from the group consisting of l-menthol, d-menthol, TK-10, MGA, l-menthyl lactate, methyl salicylate, saccharin, mannitol, sorbitol, glucose, sucrose, fructose, neohesperidin dihydrochalcone, eugenol, vanillin, thymol, CGA, and linalool;

R' and R" are independently selected from the group consisting of R, C12-C18 diacyl glycerol, partially hydrolyzed vinyl acetate-ethylene copolymer, cellulose, chitin, glucosamine, silica gel, glycerol, lower alkyl vinyl ether maleic acids, sodium, potassium, calcium, zinc, magnesium, ammonium, protonated amines, partially or fully protonated amine-containing polymers, and hydrogen;

X, X', and X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur; and

n is and integer from 1 to 3.

In addition, R' may equal R", preferably wherein R' and R" are independently selected from the group consisting of calcium, zinc, manganese, and magnesium.

Most preferred phosphate derivatives are menthyl monophosphate, eugenyl monophosphate, thymyl monophosphate, menthyl diphosphate, bis menthyl pyrophosphate, and menthyl triphosphate. "Menthol" and "menthyl" herein refer to d or l (most preferred) or racemic mixtures of d and l.

The phosphate derivatives are used in the present invention at levels of from about 0.001% to about 25%, preferably from about 0.01% to about 15%, by weight of the composition.

Carrier Materials:

In formulating the compositions of this invention the phosphate derivative will be incorporated into a carrier which may be completely inert or which may be or contain other active ingredients. The term "carrier materials", as used herein, means one or more compatible substances suitable for administration to a human or lower animal. The term "compatible", as used herein means that the components of the

compositions are capable of being commingled with phosphate derivatives, actives, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the present compositions under ordinary use situations. Carrier materials must also be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

A wide variety of carriers will be suitable depending upon the end use of the compositions. The phosphate derivatives can be incorporated into a range of compositions generally divided into oral and topical compositions, both terms being meant in their broadest possible sense. Oral compositions include not only foodstuffs and beverages taken into the mouth and swallowed, but also other orally ingested compositions taken into the mouth for reasons other than for sustenance. Such compositions include (but are not limited to) solid oral dosage forms such as tablets, tablet coatings, caplets, hydrogels, and liquid oral dosage forms such as syrups, emulsions and suspensions. Oral compositions also include those compositions which are taken into the mouth but are not necessarily swallowed, e.g. chewing gum.

Topical compositions include compositions applied to, or which in normal usage come in contact with, the internal membranes of the body such as those of the nose, mouth, or throat, whether by direct or indirect application. Such compositions include (but are not limited to) nasal sprays, dentifrices, oral rinses, lozenges, foams, gels, and throat sprays. Topical compositions may also be compositions applied to the external surfaces of the body for therapeutic reasons or reasons other than for cosmetic benefit. Such compositions include ointments, lotions, gels, and creams. Preferred compositions of the present invention are health care compositions such as dentifrices, oral rinses, liquid oral dosage forms and nasal sprays.

The present compositions preferably comprise from about 0.1% to about 99%, and preferably from about 1% to about 99%, by weight of the composition. Suitable carrier materials herein, depending on intended end use, are selected from the group consisting of solvents, suspending agents, solubilizing agents, diluents, surfactants, buffers, lubricants, thickeners, emulsifiers, flavoring agents, colorants, humectants, sweeteners, co-solvents, binders, disintegrating agents, flow-inducing agents, coolants, wetting agents, antioxidants, stabilizers, and tableting agents.

Dentifrices

Dentifrice compositions may be of the liquid, paste, powder or gel type. These compositions will usually comprise a finely divided abrasive or polishing material, e.g. precipitated chalk, silica, magnesium silicate, calcium polymetaphosphate, aluminum hydroxide or other similar materials well known in the

art. Abrasive materials are more fully described in U.S. Patent 3,070,510, Cooley et al., December 25, 1962, which is incorporated herein by reference. Toothpaste compositions additionally contain a surfactant or foaming agent. Suitable surfactants are those which are reasonably stable and foam throughout a wide pH range, including non-soap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents. These surfactants are disclosed by Gieske et al. in U.S. Patent 4,051,234, issued September 27, 1977, also incorporated herein by reference.

Optional ingredients in dentifrice compositions include flavoring agents, colorants, buffers, lubricants, thickeners, emulsifiers or plasticizers, and humectants. Dentifrice carrier materials typically comprise from about 50% to about 94%, and preferably from about 60% to about 80%, by weight of the dentifrice compositions.

Oral Rinses

Oral rinses usually comprise an aqueous, alcoholic, or aqueous-alcoholic solution of an antiseptic which is often colored or flavored for palatability. Optional ingredients include humectants, surfactants, sweeteners, emulsifying agents, fluoride ion sources, tartar control, and anti-plaque agents. Oral rinse products may also be formed by dissolving a powder or tablet containing stannous gluconate in water just prior to use.

Conventional oral rinse compositions generally comprise from about 0% to 60% ethyl alcohol, 0% to 20% of a humectant, 0% to 2% emulsifying agents, 0% to 0.5% sweetening agents, 0% to 0.3% flavoring agents and the balance water.

Liquid Oral Dosage Forms

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, pseudo emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules. These dosage forms also contain suitable solvents, emulsifying agents, buffering agents, suspending agents, diluents, natural and artificial sweeteners, coloring agents, and flavoring agents. Antioxidants such as butylated hydroxy anisole or butylated hydroxy toluene, and preservatives such as methyl or propyl paraben or sodium benzoate may also be included. Specific examples of carriers and excipients that may be used to formulate oral dosage forms, are described by Roberts in U.S. Patent 3,903,297, issued September 2, 1975, which is incorporated herein by reference.

Since many of the actives are generally used in the form of a water-soluble salt, they can be readily incorporated into conventional aqueous-based formulations. Water-insoluble or poorly soluble actives, generally in base form, may also be incorporated into aqueous-based orally acceptable carriers such as dispersions, suspensions, oil-in-water emulsions and the like by means of suitable dispersing,

suspending or emulsifying agents, respectively, which are readily apparent to those skilled in the art of formulations.

In preparing the liquid oral dosage forms, the active components are incorporated into an aqueous-based orally acceptable carrier consistent with conventional practices. An "aqueous-based orally acceptable carrier" is one wherein the entire or predominant solvent content is water. Typical carriers include simple aqueous solutions, syrups, dispersions and suspensions, and aqueous based emulsions such as the oil-in-water type. The most preferred carrier is a suspension or solution of the phosphate derivative and active in an aqueous vehicle containing a suitable suspending or solubilizing agent. Suitable suspending agents include celluloses, carboxymethyl cellulose and its salts, guar gum and the like. Suitable solubilizing agents include sucrose solutions, ethanol, and surfactants such as polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides (e.g., Polysorbate 80). Suspension systems, suspension and solubilizing agents, and methods for their use are described in M. Pernarowski, "Solutions, Emulsions and Suspensions" Remington's Pharmaceutical Sciences (A. Osol, editor, 15th Edition, 1975), which is incorporated herein by reference. While the amount of water in the compositions of this invention can vary over quite a wide range depending upon the total weight and volume of the essential ingredients and other optional ingredients, the total water content will generally range from about 20% to about 75%, and preferably from about 20% to about 40%, by weight of the composition.

Although water itself may make up the entire carrier, typical oral formulations also contain a co-solvent including but not limited to alcohol, propylene glycol, glycerin, sorbitol solution, and the like, to assist solubilization and incorporation of water-insoluble ingredients, flavoring oils and the like into the composition. In general, the compositions preferably contain from about 5 to about 25 volume/volume percent of the co-solvent, most preferably from about 10 to about 20 volume/volume percent of the co-solvent.

Nasal Sprays

Carriers suitable for nasal administration provide a product which is delivered to the nasal passages. Such carriers may be for example, aqueous or aerosol and are more fully described in Remington's Pharmaceutical Sciences (17th Edition, 1985), which is incorporated herein by reference. Such product forms include (but are not limited to) nasal solutions for use as drops or as sprays, nasal suspensions, nasal ointments, nasal gels, or other vehicles suitable for nasal administration.

Preferred nasal dosage forms are solutions, suspensions, and gels, which normally contain sodium chloride in a major amount of water (preferably purified

water). Other ingredients including but not limited to: pH adjusters such as sodium hydroxide; emulsifiers or dispersing agents; buffering agents such as sodium bicarbonate; preservatives such as benzyl alcohol, parabens, benzalkonium chloride, chlorhexidine gluconate and disodium EDTA; agents for regulating isotonicity such as sodium chloride, boric acid, potassium phosphate and propylene glycol; wetting agents; thickening agents such as methylcellulose, zanthan gum, carboxymethyl cellulose, and carbomer; humectants such as sorbitol, propylene glycol, sorbitol, and glycerol; surfactants such as polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides; and mixtures thereof, may also be present.

Solid Oral Dosage Forms

The present composition may also be in a solid oral dosage form. Tablets can be compressed, triturated, freeze dried, sugar-coated, film-coated or multiple compressed. The tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents. In general, carrier materials suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms", Modern Pharmaceutics, volume 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated herein by reference. Techniques and compositions for making tablets, capsules, and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

Lozenges and Chewing Gums

Other embodiments of the subject invention include lozenges and chewing gums. Lozenge compositions comprise a lozenge carrier (i.e. a candy base). Candy bases are disclosed in U. S. Patent 4,472,373, Ryan, issued September 18, 1984, and in U.S. Patent 4,083,955, Grabenstetter et al., issued April 11, 1978. Chewing gum compositions comprise a chewing gum carrier such as those which are disclosed in these same patents, both of which are incorporated herein by reference. Chewing gum carriers may comprise, for example, a gum base, flavoring agents, and sweetening agents.

Other Carriers

The invention compositions may be formulated with a wide variety of carrier materials in addition to those already disclosed. Some examples of substances which can serve as carrier materials are sugars such as lactose, glucose, and sucrose;

starches such as cornstarch and potato starch; cellulose and its derivatives such as sodium carboxymethylcellulose, ethylcellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; stearic acid; magnesium stearate; dicalcium phosphate; calcium sulfate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; agar; alginic acid; as well as other non-toxic compatible substances used in consumer or health care formulations.

Coolant materials may also be included as carrier materials in the invention compositions. Preferred coolants in the present compositions are the paramenthane carboxyamide agents such as N-ethyl-p-menthane-3-carboxamide (known commercially as "WS-3"), and 3-l-menthoxypropane-1,2-diol (known commercially as "TK-10"), and mixtures thereof. These coolants are described in PCT Patent Application Publication WO 92-17164, to Upson et al., published October 15, 1992. TK-10 is also described in U.S. Patent 4,459,425 to Amano et al., issued July 10, 1984; and WS-3 and the paramenthane carboxyamide agents are also described in U.S. Patent 4,136,163 to Watson et al., issued January 23, 1979. The disclosures of all three of these patent publications are incorporated by reference herein in their entirety.

When desired or necessary, suitable binders, lubricants, and disintegrating agents can also be incorporated in the compositions. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia sodium alginate, carboxymethylcellulose, microcrystalline cellulose, polyethylene glycol and waxes. Lubricants may include, for example, starch, methylcellulose, agar, bentonite, guar gum, etc. Wetting agents such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, sweetening agents, excipients, tableting agents, stabilizers, antioxidants, and preservatives can also be present.

Active:

The invention compositions may also contain a safe and effective amount of one or more actives. Some actives that are useful in these compositions include (but are not limited to) antimicrobial agents such as iodine, sulfonamides, mercurials, bisbiguanides, or phenolics; antibiotics such as tetracycline, neomycin, kanamycin, metronidazole, or clindamycin; anti-inflammatory agents such as aspirin, acetaminophen, naproxen, ibuprofen, flurbiprofen, indomethacin, eugenol, or hydrocortisone; immune-suppressive or stimulatory agents such as methotrexate or levamasole; dentinal desensitizing agents such as potassium nitrate, strontium chloride or sodium fluoride; odor masking agents such as peppermint oil or

chlorophyll; immune reagents such as immunoglobulin or antigens; local anesthetic agents such as lidocaine or benzocaine; nutritional agents such as amino acids, essential fats, vitamins and minerals; antioxidants such as thymol, alphatocopherol and butylated hydroxy toluene; lipopolysaccharide complexing agents such as polymyxin; quaternary ammonium compounds such as benzalkonium chloride and cetyl pyridinium chloride; aromatics such as camphor, eucalyptus oil, and aldehyde derivatives such as benzaldehyde; denture adhesives such as lower alkyl vinyl ether-maleic acid or anhydride copolymers and their salts; coolants having therapeutic efficacy such as menthol; or peroxides such as urea peroxide. It is recognized that in certain forms of therapy, combinations of these agents in the same delivery system may be useful in order to obtain an optimal effect. Thus, for example, an antimicrobial and an anti-inflammatory agent may be combined in a single delivery system to provide combined effectiveness. Preferred actives are nutritional, therapeutic, medicinal, pharmaceutical, and those commonly used in health care products.

Preferred formulations for the present invention compositions which comprise one or more actives are dental care preparations such as dentifrices and oral rinses, and cough/cold preparations in liquid oral dosage forms. Actives commonly utilized in cough/cold preparations include but are not limited to decongestants such as pseudoephedrine hydrochloride, phenylpropanolamine HCl, pseudoephrine hydrochloride and ephedrine hydrochloride; antitussives such as dextromethorphan, chlophedianol, carbetapentane, noscapine, codeine, hydrocodone, hydromorphone; analgesics such as acetaminophen and ibuprofen; expectorants or mucolytics such as glyceryl guaiacolate, guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and ambroxol; antihistamines such as chlorpheniramine maleate, azatadine, doxylamine succinate, brompheniramine maleate and diphenhydramine hydrochloride; and non-sedating antihistamines such as astemizole, acrivastine, ketotifen, and terfenadine. These components as well as others are described in the following: U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, and U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988 which are incorporated herein by reference. Also useful are bronchodilators such as theophylline and albuterol; and stimulants such as caffeine.

Oral forms of cough/cold preparations comprise a safe and effective amount of one or more active components. Solid oral dosage forms preferably contain from about 5% to about 95%, more preferably from about 10% to about 95%, and most preferably from about 25% to about 95%, of the active components. Liquid oral dosage forms preferably contain from about 1% to about 50%, more preferably from

about 1% to about 25%, and most preferably from about 3% to about 10%, of the active components.

Dental care preparations typically comprise a soluble fluoride ion source as one of the actives. The soluble fluoride ion source is used in an amount sufficient to provide from about 10 to about 5000 ppm of the fluoride ion. Preferred fluorides are sodium fluoride, stannous fluoride, inidium fluoride, and sodium monofluorophosphate. Norris et al., U.S. Patent 2,946735, issued July 26, 1960 and Widder et al., U.S. Patent 3,678,154, issued July 18, 1972, disclose such salts as well as others. Both patents are incorporated herein by reference in their entirety.

Various polymers and mixtures thereof are also useful in dental care preparations. These polymers may be synthetic anionic polymeric polycarboxylates and their complexes and/or carboxyvinyl polymers. Polymers useful in the present compositions are disclosed in U.S. Patent 4,906,456 to Gaffer et al., issued March 6, 1990, incorporated herein by reference in its entirety.

Pyrophosphate salts are pharmaceutical actives that may also be included in dental care preparations. Any of the alkali metal pyrophosphate salts may be used in either their hydrated or unhydrated forms. Specific salts include tetra alkali metal pyrophosphate, dialkali metal diacid pyrophosphate, trialkali metal monoacid pyrophospate and mixtures thereof, wherein the alkali metals are preferably sodium or potassium. Pyrophosphate salts are described in more detail in Kirk & Othmer, Encyclopedia of Chemical Technology, Second Edition, Volume 15, Interscience Publishers (1968), incorporated herein by reference in its entirety. The amount of pyrophosphate salt useful is any effective amount and is generally enough to provide at least 1.0% $P_2O_7^{-4}$, preferably from about 1.5% to about 6%, and more preferably from about 3.5% to about 6%, to the compositions. It is to be appreciated that the level of $P_2O_7^{-4}$ is that capable of being provided to the composition (i.e., the theoretical amount at an appropriate pH) and that other pyrophosphate forms (e.g., $HP_2O_7^{-3}$) may be present when a final product is established.

Anti-plaque and anti-gingivitis pharmaceutical actives may also be included in the dental preparations. These actives include quaternary ammonium compounds or bis-biguanides such as chlorhexidine and stannous ion in the form of a combination of stannous fluoride and stannous gluconate. Oral compositions comprising stannous ion are described fully in U.S. Patent 5,004,597 to Majeti et al., issued April 2, 1991, incorporated herein by reference in its entirety. Disinfectant agents like triclosan and antiseptic agents like thymol may also be included in the dental preparations.

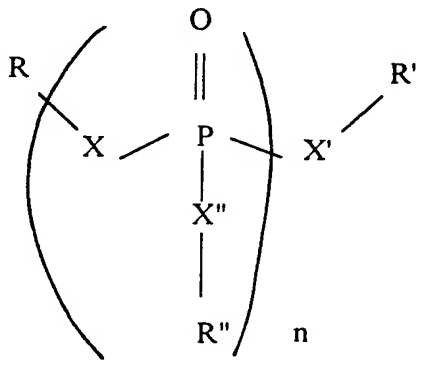
Pharmaceutical actives commonly utilized in gastrointestinal products are those agents which are safe and effective when administered orally for treating

disorders of the upper gastrointestinal tract which result in symptoms of upper gastrointestinal tract distress. Compositions for relieving gastrointestinal distress may include antacid agents, acid secretion prevention agents, other pharmaceutical actives and mixtures thereof.

Antacid agents include aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium alumino silicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, sodium bicarbonate, and mixtures thereof. Acid secretion prevention agents include cimetidine, ranitidine, famotidine, omeprazole, and mixtures thereof. Other useful pharmaceutical actives include antiflatulent agents such as simethicone and bismuth-containing agents such as, bismuth subsalicylate, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subcarbonate, bismuth subgalate, and mixtures thereof. The pharmaceutical actives comprise from about 1% to about 99%, and preferably from about 25% to about 60% by weight of the composition.

Pyrophosphate Dies[illegible] Oral Compositions

A second d[illegible]ry concerns a tartar control oral composition containing carrier material and a specific type of pyrophosphate compound(s) of the formula below, wherein the composition is in a form which is suitable for oral administration.. The pyrophosphate compound has the following formula:



where R and R' are independently selected from the group consisting of a coolant component, a sweetener component, an antimicrobial agent and a flavorant component; and where R and R' is hydrogen,

each R" is independently selected from the group consisting of R and R", an adherent group, M+, M++, C+, and hydrogen;

X, X', and X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

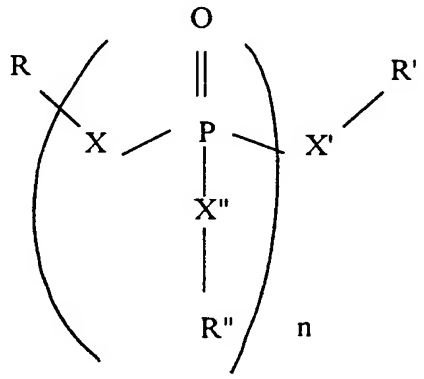
n is an integer greater than or equal to 1;

M+ and M++ are physiologically relevant metal cations; and

C+ is an organic cation; and

These terms are described above.

Preferred pyrophosphate derivatives have the formula:



In the above formula:

R and R' are independently selected from the group consisting of 1-menthol, d-menthol, TK-10, MGA, 1-menthyl lactate, methyl salicylate, saccharin, mannitol, sorbitol, glucose, sucrose, fructose, neohesperidin dihydrochalcone, eugenol, vanillin, thymol, CGA, and linalool;

each R" is selected from the group consisting of R and R', C12-C18 diacyl glycerol, partially hydrolyzed vinyl acetate-ethylene copolymer, cellulose, chitin, glucosamine, silica gel, glycerol, lower alkyl vinyl ether maleic acids, sodium, potassium, calcium, zinc, magnesium, ammonium, protonated amines, partially or fully protonated amine-containing polymers, and hydrogen;

X, X', and X" are independently selected from the group consisting of oxygen (preferred), nitrogen, and sulfur; and

n is an integer from 2 (preferred) to 3.

"Menthol" and "menthyl" herein refer to d or l (most preferred) or racemic mixtures of d and l.

R and R' groups can be the same as or different (preferred) from each other. The R and R' components can be various combinations, depending upon whether a cooling, flavoring, sweetening, and/or antimicrobial effect is desired. R or R' is preferably a flavorant component selected from the group consisting of menthol, methyl salicylate, eugenol, vanillin, thymol, cinnamaldehyde glycerol acetal , and linalool.

When R or R' is a flavorant or sweetener or antimicrobial, the other R or R' is a coolant component selected from the group consisting of l-menthol, d-menthol, 3-l-menthoxypropane-1,2-diol ("TK-10"), menthone glycerol acetal ("MGA"), and l-menthyl lactate.

When R or R' is a flavorant or coolant or sweetener, the other R or R' is an antimicrobial component preferably selected from the group consisting of 2,4,4'-trichloro-2'-hydroxy-diphenyl ether, 2-phenoxyethanyl, chlorhexidine, and thymol.

When R or R' is flavorant or coolant or sweetener, the other R or R' is alternatively and preferably an antimicrobial component selected from the group consisting of 2,4,4'-trichloro-2'-hydroxy-diphenyl ether ; 2-phenoxyethanol; 1,1-hexamethylene bis [5-(p-chlorphenyl) biguanidine] di-D-gluconate; and thymol. Most preferred is 2,4,4'-trichloro-2'-hydroxy-diphenyl ether.

When R or R' is flavorant or antimicrobial or coolant, the other R or R' alternatively is a sweetener component selected from the group consisting of saccharin, mannitol, sorbitol, glucose, sucrose, fructose, and neohesperidin dihydrochalcone.

The present invention also includes the instance where one R group acts both as an antimicrobial and a flavorant or coolant.

Mixed pyrophosphate diesters are also included herein, ie, where the compound contains one R group which is a coolant and one R group which is a flavor. The mixed pyrophosphate compound, then, provides three benefits: tartar control, flavor and cooling. Alternatively, one R group can be a flavor or coolant and the other R group can be a safe, hydroxyl-containing antimicrobial group. If an antimicrobial group is included, three benefits can be achieved by inclusion of only this one type of active in the oral composition: good taste (coolant/flavor), tartar control and antimicrobial effect. Without meaning to be bound by theory, this compound is believed to lead to a reduction in plaque formation on the teeth and/or a decrease in the incidence and/or severity of gingivitis and/or prevention or reduction of mouth odor. Further without meaning to be bound by theory, it is believed that

the tartar control effect is achieved by the parent compound or by inorganic pyrophosphate which is released when the parent compound is cleaved by phosphatase enzyme present in the oral cavity.

When thymol in particular is included as one of the R groups, both a flavor effect and a low level antimicrobial effect are conveyed in addition to tartar control. If the other R group is then a coolant, a fourth benefit (cooling taste) is believed to be conveyed.

Compounds of this type may provide antitartar activity without attendant unpleasant taste. Oral compositions containing pyrophosphates can convey a bitter taste. A pyrophosphate such as this one which can control tartar and at the same time taste good (or have improved taste) is surprising and beneficial.

Another advantage of this compound is that a single compound can provide multiple benefits: tartar control, improved taste (cooling and/or flavoring and/or sweetening) and/or an antimicrobial effect.

It is also believed that one or more of these four effects, cooling, flavor, antimicrobial, and tartar control, may surprisingly be sustained effects. Here, "sustained" means that one or more of these effects continues for some time after administration or use of the oral composition containing the present pyrophosphate diesters. Thus, compound remaining in the oral cavity, for example, adhered either on the plaque itself or on the teeth, would continue to be cleaved by phosphatase enzyme, which is commonly present in saliva and in plaque. As the compound is broken down, the coolant, flavor, tartar control, and/or antimicrobial effect would continue, likely at a low but noticeable level. It can also be called an "extended" effect, as in "extended cooling". By phosphatase enzyme is meant acid or alkaline phosphatases and pyrophosphatases.

Preferred is from about 0.01% to about 15%, more preferably from about 0.05% to about 10%, most preferably from about 0.5 to about 5%, by weight of the composition, of the pyrophosphate compound. Also preferred is from about 85% to about 99.99%, more preferably from about 90% to about 99.05%, most preferably from about 95% to about 99.5%, by weight of the composition, of carrier material.

The oral composition herein is preferably toothpaste (most preferred), mouthrinse, or liquid dentifrice. Sodium fluoride is preferably included in dentifrice compositions herein. Components to be added should be safe for oral use. By "safe" is meant without undue adverse side effects (such as toxicity, irritation or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention.

Preferred pyrophosphate diesters are selected from the group consisting of 1,2-bis-menthyl-dihydrogen pyrophosphate; 1,2-bis-thymyl-dihydrogen pyrophosphate, 1,2-bis-vanillyl-dihydrogen pyrophosphate, 1,2-bis-eugenyl-dihydrogen pyrophosphate, 1,2-bis-methyl salicylyl-dihydrogen pyrophosphate; and mixtures thereof. More preferred are 1,2-bis-[3-methyl-6-isopropyl-cyclohexyl]-dihydrogen pyrophosphate (or 1,2-bis-menthyl-dihydrogen pyrophosphate); and 1,2-bis-thymyl-dihydrogen pyrophosphate. Most preferred is 1,2-bis-[3-methyl-6-isopropyl-cyclohexyl]-dihydrogen pyrophosphate.

Also preferred are the "mixed pyrophosphate diesters", which include 1-thymyl-2-menthyl-dihydrogen pyrophosphate; 1-(3-1-menthoxypropane-1,2-diol)-2-thymyl-dihydrogen pyrophosphate; 1-(2,4,4'-trichloro-2'-hydroxy-diphenyl ether)-2-eugenyl-dihydrogen pyrophosphate; 1-eugenyl-2-thymyl-dihydrogen pyrophosphate; and 1-menthyl-2-methyl salicylyl-dihydrogen pyrophosphate. Of those, the more preferred are 1-thymyl-2-menthyl-dihydrogen pyrophosphate and 1-(3-1-menthoxypropane-1,2-diol)-2-thymyl-dihydrogen pyrophosphate.

Additional ingredients suitable for use in an oral composition can be included in the present compositions. These are described above. Ingredients which interfere with or block the effects of the present compounds are preferably not included.

The most preferred compound for use herein is 1,2-bis-[3-methyl-6-isopropyl-cyclohexyl]-dihydrogen pyrophosphate or 1,2-di-[(1R)-menthyl]-dihydrogen pyrophosphate $C_{20}H_{40}O_7P_2$ (here called "BMPP"). This chemical compound is included in Milobedzki and Janczak, Roczniki Chem. 11 [1931] 840 and Jacobsohn, Comptes Rendu Soc. Biol., 104 [1930] 432; Biol. J., 230 [1931] 304, which are incorporated herein by reference.

It has been found in the present invention that BMPP, which has a menthol component, when taken into the oral cavity in, for example, a mouthrinse, has a sweet initial flavor and a surprisingly long lasting (eg, up to one hour and perhaps beyond) cooling effect. This flavor was quite surprising since pyrophosphates and menthol are known to have an unpleasant taste. BMPP is also believed to reduce and/or prevent tartar formation.

BMPP can be synthesized by coupling the phosphate, menthyl monophosphate ("MMP"), via a dehydration reaction using dicyclohexylcarbodiimide ("DCC"). Other compounds herein can also be made using dehydration reactions. Alternatively, BMPP can be synthesized by reacting MMP with an intermediate formed in the preparation of MMP.

Also included herein is a method of reducing tartar by applying to the dental enamel the above described oral composition. Also included is a method of creating

a sustained cooling, sweetening, flavoring or antimicrobial effect in the oral cavity and adjoining areas of the body by applying to the dental enamel an oral composition according to the above-described composition. Also included is a method of reducing or preventing plaque or gingivitis or mouth odor by applying to the dental enamel an oral composition according to he above-described composition.

The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the present invention. Percentages are by weight unless otherwise stated.

Example I

Toothpaste Composition

A toothpaste composition according to the present invention is prepared having the following components:

Component	Weight %
Eugenol Monophosphate	0.300
Purified Water	10.422
Sorbitol	60.565
Sodium Fluoride	0.243
Saccharin	0.130
Colorant	0.500
Silica	20.000
Spearmint Flavor	0.500
Carbopol 934	0.300
Xanthan Gum	0.475
Trisodium Phosphate	1.450
Monosodium Phosphate	0.590
Sodium Alkyl Sulfate Solution (27.9% in H_2O)	4.000
Titanium Dioxide	0.525

Add sorbitol to water and mix. Dissolve salts, eugenol monophosphate, sodium fluoride, saccharin, tridosium phosphate, monosodium phosphate, and then add colorant. Adjust to pH 7.0. Separately combine silica, carbopol, and xanthan gum and then slowly add this mixture to the composition while mixing continuously. Add sodium alkyl sulfate. Add spearmint flavor. Mix for ten more minutes.

Example II

Oral Mouth Rinse Composition

An oral mouth rinse composition according to the present invention is prepared having the following components:

Component	Weight %
Thymol Monophosphate	0.300
Ethanol (190 proof)	16.250
Polysorbate 80	0.120
Glycerin	10.000
Purified Water	73.1218
Benzoic Acid	0.0045
Cetylpyridinium Chloride	0.045
Domiphen Bromide	0.005
Sodium Saccharin	0.060
Colorant	0.040
Sodium Benzoate	0.0537

To ethanol, add all ingredients except thymol monophosphate and mix for 5 minutes. Add thymol monophosphate last and then adjust the pH of the composition to pH 6.0.

Example III

Liquid Oral Dosage Form

A liquid oral dosage form composition according to the present invention is prepared having the following components:

Component	Weight %
Menthyl Triphosphate	0.300
Sucrose (xfine granular)	51.000
Polysorbate 80	0.020
Glycerin	2.000
Propylene Glycol	15.000
Sodium Citrate, dihydrate	0.522
Citric Acid	0.338
Potassium Sorbate	0.100
Dextromethorphan Hydrobromide	0.133
Guaifenesin	1.333
Flavor	0.300
Distilled Water	18.954
Alcohol	10.000

Mix together sucrose and about 1/3 the amount of water and heat to about 60oC until sucrose is dissolved. Mix in polysorbate 80 and glycerin. Separately mix together propylene glycol, sodium citrate dihydrate, menthyl monophosphate citric acid and about 1/3 the amount of water. Separately mix together potassium sorbate and about 1/3 the amount of water. Add flavor. Mix together sucrose solution with propylene glycol solution. Mix together this solution and potassium sorbate solution. Lastly, add flavor solution. Adjust water level for proper batch size. Adjust pH to about 6.0. Mix for 30-35 minutes.

Example IV

Chewable Tablet

A chewable tablet composition according to the present invention is prepared having the following components:

Component	Weight %
Calcium Carbonate and mannitol (50:50 wgt ratio)	88.0
Powdered Mannitol	4.785
Aspartame	0.178
Sodium Saccharin	0.092
Prosweet	0.300
3-l-menthoxypropane-1,2-diol	0.300
N-ethyl-p-menthane-3-carboxamide	0.025
Menthyl monophosphate (a)	0.300
Peppermint Flavor	0.400
Vanilla flavor	0.300
Cola flavor	0.070
Blue speckles	0.750
Talc	2.000
Magnesium Stearate	2.500

(a) prepared as described below

Mill N-ethyl-p-menthane-3-carboxamide to assure that it is in powder form. Dry mix all ingredients, except magnesium stearate, until uniformly mixed. Add magnesium stearate and mix for 1-2 minutes. Press desired amount into tablet (target is 550 mg/tablet).

Preparation of Menthyl Monophosphate

In a two-liter, three-neck round bottom flask cooled in an ice/water bath and equipped with a mechanical stirrer and an addition funnel, 153 ml of triethylamine is added to 157 g. of menthol in 186 ml of phosphorus oxychloride. After allowing the

stirred suspension to warm to room temperature over 1 hour, the mixture is recooled to OC, 500 ml of ether is added, and the mixture is carefully hydrolyzed with 500 ml of water. After 1.5 hours at 0C, the mixture is allowed to warm to room temperature overnight. The aqueous layer is then extracted with ether (3 x 500 ml) and the combined ether layers are extracted with a 1 N sodium hydroxide solution (4 x 1 l.). After back-extracting the combined basic extracts with more ether (2 x 500 ml), the basic solution is acidified with concentrated hydrochloric acid solution to pH 0. A yellow, oily product is removed and the remaining aqueous layer is extracted with three, one-liter portions of ether. The oil is dissolved in the combined ether extracts, the ether solution is dried with sodium sulfate, the mixture is filtered, and the solution is concentrated under vacuum to give a viscous syrup. After drying the product further in a vacuum oven, a white powder is obtained which can be purified by crystallization from an acetone/water mixture.

Example V

Toothpaste Composition

A toothpaste composition according to the present pyrophosphate diester invention is prepared having the following components:

Component	Weight %
BMPP*	1.00
Purified Water	Balance
Sorbitol	60.565
Sodium Fluoride (1100 ppm F^-)	0.243
Saccharin	0.130
Colorant	0.500
Silica	20.000
Flavor	0.500
Carboxymethyl cellulose	0.300
Xanthan Gum	0.475
Trisodium Phosphate	1.450
Monosodium Phosphate	0.590
Sodium Alkyl Sulfate Solution (27.9% in H_2O)	4.000
Titanium Dioxide	0.525

*=1,2-bis-[3-methyl-6-isopropyl-cyclohexyl]-dihydrogen pyrophosphate

Add sorbitol to water and mix. Dissolve salts, BMPP, sodium fluoride, saccharin, trisodium phosphate, and monosodium phosphate. Adjust the pH to 7.0 and then add colorant. Separately combine silica, carboxymethyl cellulose, and

xanthan gum and then slowly add this mixture to the composition while mixing continuously. Add sodium alkyl sulfate. Add the flavor (eg, spearmint, peppermint, wintergreen, fruit) to the composition and mix for ten more minutes.

Preparation of BMPP

One mole of menthyl monophosphate (MMP) is reacted with two moles of dicyclohexylcarbodiimide (DCC) in tetrohydrofuran (THF). Excess DCC is hydrolyzed with water and the insoluble dicyclohexylurea byproduct is removed by filtration. The THF is removed under vacuum and the product is extracted into ethyl ether. The ethyl ether is dried with anhydrous sodium sulfate, the mixture is filtered and the solution is concentrated under vacuum to give a white solid. The product is recrystallized in wet ethyl acetate and dried in a vacuum oven then any remaining MMP is removed with an acetone wash.

Example VI

Oral Mouth Rinse Composition

An oral mouth rinse composition according to the present pyrophosphate diester invention is prepared having the following components:

Component	Weight %
BMPP*	1.00
Ethanol (190 proof)	16.250
Polysorbate 80	0.120
Glycerin	10.000
Purified Water	Balance
Benzoic Acid	0.0045
Cetylpyridinium Chloride	0.045
Domiphen Bromide	0.005
Sodium Saccharin	0.060
Colorant	0.040
Sodium Benzoate	0.0537

*=1,2-bis-[3-methyl-6-isopropyl-cyclohexyl]-dihydrogen pyrophosphate

To ethanol, add all ingredients except BMPP and mix for 5 minutes. Add BMPP last and then adjust the pH of the composition to pH 6.0.

Other pyrophosphate diester compounds of the present invention can be substituted for the BMPP above, such as 1,2-bis-thymyl-dihydrogen pyrophosphate, 1,2-bis-vanillyl-dihydrogen pyrophosphate, 1,2-bis-eugenyl-dihydrogen pyrophosphate, and 1,2-bis-methyl salicylyl-dihydrogen pyrophosphate. The amount

of the pyrophosphate diester employed in the composition can vary within the limit described herein.

Example VII

Oral Mouth Rinse Composition

An oral mouth rinse composition according to the present pyrophosphate diester invention is prepared having the following components:

Component	Weight %
Mixed pyrophosphate diester*	1.0
Ethanol (190 proof)	16.250
Polysorbate 80	0.120
Glycerin	10.000
Purified Water	Balance
Benzoic Acid	0.0045
Cetylpyridinium Chloride	0.045
Domiphen Bromide	0.005
Sodium Saccharin	0.060
Colorant	0.040
Sodium Benzoate	0.0537

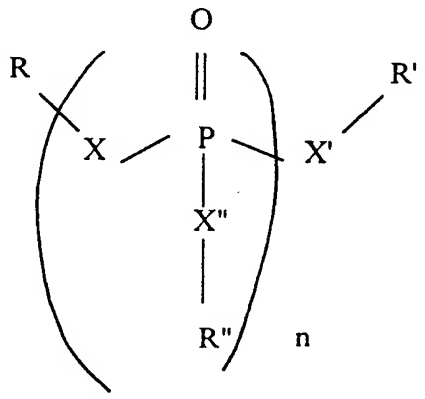
*=1-menthyl-2-(2,4,4'-trichloro-2'-hydroxy-diphenyl ether)-dihydrogen pyrophosphate

To ethanol, add all ingredients except the mixed phosphate ester and mix for 5 minutes. Add the mixed phosphate ester last and then adjust the pH of the composition to pH 6.5.

Other pyrophosphate diester compounds of the present invention can be substituted for the one above, such as 1-thymyl-2-menthyl-dihydrogen pyrophosphate; 1-(3-1-menthoxypropane-1,2-diol)-2-thymyl-dihydrogen pyrophosphate; 1-(2,4,4'-trichloro-2'-hydroxy-diphenyl ether)-2-eugenyl-dihydrogen pyrophosphate; 1-eugenyl-2-thymyl-dihydrogen pyrophosphate; and 1-menthyl-2-methyl salicylyl-dihydrogen pyrophosphate.

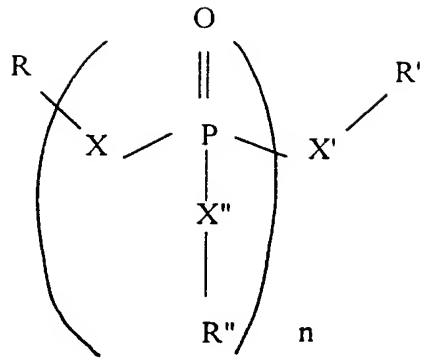
What is claimed is

1. A tartar control oral composition, comprising, by weight of the composition:
(a) from 0.001% to 20% of one or more compounds of the formula;



where R and R' are independently selected from the group consisting of a coolant component, a sweetener component, an antimicrobial agent and a flavorant component and where R or R' is hydrogen;
each R" is independently selected from the group consisting of R and R", an adherent group, M+, M++, C+, and hydrogen;
X, X', and X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur;
n is an integer greater than or equal to 2;
M+ and M++ are physiologically relevant metal cations; and
C+ is an organic cation; and
(b) from 80% to 99.999% of a carrier material;
and wherein further the composition is in a form suitable for oral administration.

2. The composition according to Claim 1 wherein the pyrophosphate compound has the formula:



where R and R' are independently selected from the group consisting of l-menthol; d-menthol; l-menthol; d-menthol; 3-l-r ..nthoxypropane-1,2-diol; menthone glycerol acetal; l-menthyl lactate; methyl salicylate; saccharin; mannitol; sorbitol; glucose; sucrose; fructose; neohesperidin dihydrochalcone; eugenol; vanillin; thymol; cinnamaldehyde glycerol acetal; and linalool;

each R" is selected from the group consisting of R and R', C12-C18 diacyl glycerol, partially hydrolyzed vinyl acetate-ethylene copolymer, cellulose, chitin, glucosamine, silica gel, glycerol, lower alkyl vinyl ether maleic acids, sodium, potassium, calcium, zinc, magnesium, ammonium, protonated amines, partially or fully protonated amine-containing polymers, and hydrogen;

X, X', and X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur; and

n is an integer from 2 to 3.

3. The composition according to any of the preceding claims wherein R or R' is a flavorant component selected from the group consisting of methyl salicylate, eugenol, vanillin, thymol, cinnamaldehyde glycerol acetal , and linalool.

4. The composition according to any of the preceding claims wherein the pyrophosphate compound is selected from the group consisting of 1,2-bis--dihydrogen pyrophosphate; 1,2-bis-thymyl-dihydrogen pyrophosphate, 1,2-bis-vanillyl-dihydrogen pyrophosphate, 1,2-bis-eugenyl-dihydrogen pyrophosphate, 1,2-bis-methyl salicylyl-dihydrogen pyrophosphate; and mixtures thereof.

5. The composition according to any of the preceding claims wherein the pyrophosphate compound is 1,2-bis-menthyl-dihydrogen pyrophosphate or 1,2-bis-thymyl-dihydrogen pyrophosphate.

6. The composition according to any of the preceding claims wherein the other R or R' is an antimicrobial component selected from the group consisting of 2,4,4'-trichloro-2'-hydroxy-diphenyl ether, 2-phenoxyethanol, chlorhexidine, and thymol.

7. The composition according to any of the preceding claims comprising from 0.01% to 15%, preferably from 0.05% to 10%, of the pyrophosphate compound and from 85% to 99.99%, preferably from 90% to 99.05%, of carrier material.

8. The composition according to any of the preceding claims comprising from 0.5% to 5% of 1,2-bis-menthyl-dihydrogen pyrophosphate.

9. The composition according to any of the preceding claims comprising a calcium or sodium salt of the pyrophosphate compound.

10. The composition according to any of the preceding claims wherein the other R or R' is selected from the group consisting of 2,4,4'-trichloro-2'-hydroxy-diphenyl ether ; 2-phenoxyethanol; 1,1-hexamethylene bis [5-(p-chlorphenyl) biguanidine] di-D-gluconate; and thymol.

11. The composition according to any of the preceding claims comprising 1-thymyl-2-menthyl-dihydrogen pyrophosphate or 1-(3-1-menthoxypropane-1,2-diol)-2-thymyl-dihydrogen pyrophosphate.

12. The composition according to any of the preceding claims wherein the composition is in the form of an oral mouth rinse, a toothpaste, or a liquid dentifrice.

13. The composition according to any of the preceding claims wherein the other R or R' is a coolant component selected from the group consisting of 1-menthol, d-menthol, 3-l-menthoxypropane-1,2-diol, menthone glycerol acetal, and 1-menthyl lactate.

14. The composition according to any of the preceding claims wherein the other R or R' is a sweetener component selected from the group consisting of

saccharin, mannitol, sorbitol, glucose, sucrose, fructose, and neohesperidin dihydrochalcone.

15. A method of reducing tartar by applying to the dental enamel an oral composition according to any of the preceding claims.

16. A method of reducing or preventing plaque or gingivitis or mouth odor by applying to the dental enamel an oral composition according to any of the preceding claims.

17. A method of creating a sustained cooling, sweetening, flavoring or antimicrobial effect in the oral cavity and adjoining areas of the body by applying to the dental enamel an oral composition according to any of the preceding claims.

INTERNATIONAL SEARCH REPORT

Intern. ..al Application No
PCT/US 94/10227

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 254 452 (LION CORP.) 27 January 1988	
A	US,A,4 448 766 (MORTON) 15 May 1984	
A	US,A,3 595 957 (MUHLER) 27 July 1971	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
21 December 1994	04.01.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Klaver, T

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte.. .onal Application No
PCT/US 94/10227

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0254452	27-01-88	JP-A- 63030408	09-02-88
		DE-D- 3788310	13-01-94
		US-A- 4913895	03-04-90
US-A-4448766	15-05-84	NONE	
US-A-3595957	27-07-71	NONE	